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Original Report

Modeled risk of ischemic heart disease following left breast irradiation with deep inspiration breath hold

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Abstract

Purpose: Deep inspiration breath hold (DIBH) dramatically reduces radiation dose to the heart during radiation therapy (RT) for left-sided breast cancer, but the subsequent risk of radiation-related ischemic heart disease (IHD) is unknown. Our primary objective was to quantify the risk of IHD following RT with DIBH using modeled risk estimates (MRE).

Methods and materials: Patients with stage 0-III left-sided breast cancer who received RT with DIBH were retrospectively studied. Computed tomography simulations were performed with DIBH and during free breathing (FB) for comparison of dosimetry. Patients were classified as high risk, at risk, or at optimal risk for IHD and baseline risk estimates for IHD were obtained from historic controls. The excess relative risk of IHD because of left breast RT was calculated using patient-specific dosimetry and an existing dose-effect model. MRE were determined from the sum of baseline risk estimates and excess risk.

Results: Between 2002 and 2011, 111 patients were treated using DIBH and 104 were available for analysis. MRE for 10-year risk of IHD with DIBH and FB were 3.25% (interquartile range [IQR], 1.20-3.44) and 3.64% (IQR, 1.43-3.81) ($P < .0001$), respectively. MRE for lifetime risk of IHD with DIBH and FB were 9.71% (IQR, 1.98-16.62) and 10.28% (IQR, 2.05-16.97) ($P < .0001$), respectively. MRE were significantly reduced by use of DIBH in all risk groups. The largest absolute risk reduction resulting from the DIBH technique was observed in patients at high risk for IHD. The median relative risk reduction in MRE resulting from DIBH was 11.4% (range, 0-32.0) and 6.4% (range, 0-23.4) at 10 years and throughout the patients' lifetime, respectively. After a median follow-up of 7.0 years (range, 1.3-11.2), the estimated 10-year freedom from IHD was 99.0% (95% confidence interval 93.4-99.8).

Conclusions: RT with DIBH may provide breast cancer survivors a clinically significant reduction in the risk of IHD.

Note—Earn CME credit by taking a brief online assessment at https://www.astro.org/JournalCME.

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Introduction

Adjuvant radiation therapy (RT) plays a vital role in the treatment of breast cancer because it improves both local control and overall survival.[1,2] However, incidental radiation dose to the heart during tangential RT has been associated with excess risk of cardiac morbidity and mortality. Ischemic heart disease (IHD) is the principal cardiac toxicity following breast RT, with the potential to reduce the overall survival benefit resulting from adjuvant RT.[2-6]

Minimization of late, radiation-related adverse effects such as IHD is an increasingly important aspect of breast cancer survivorship. A recent retrospective, case–control study reported that the excess risk of IHD following breast RT is proportional to the mean heart dose (MHD), is apparent within 4 years, and persists for decades regardless of existing cardiac risk factors. Specifically, this relative risk is linearly dependent on MHD at a rate of 16.3%, 15.5%, and 7.4% per Gy within years 0-4, years 5-10, and 20-plus years following RT, respectively.[6] Therefore, minimizing exposure to the heart might provide a clinical benefit, particularly in women with left-sided breast cancer.

Use of the deep inspiration breath hold (DIBH) technique can dramatically reduce the MHD by immobilizing the chest wall and optimizing its distance from the heart.[7,8] Despite this dosimetric benefit, randomized data do not support that DIBH protects the heart from radiation damage.[9] However, the true risk of radiation-related IHD following RT with DIBH is unknown because the current data are limited to surrogate endpoints such as dosimetry and cardiac imaging.[7-9] Therefore, we aimed to quantify the effect that the DIBH technique has on the risk of IHD using modeled risk estimates (MRE). To corroborate findings, a secondary aim was to quantify the 10-year risk of IHD in a cohort with long-term follow-up.

Methods and materials

Following approval by the Institutional Review Board, the medical records of patients treated with DIBH were studied. Included patients were consecutively treated with RT to the left breast or chest wall between 2002 and 2011; however, patients with less than 1 year of follow-up were excluded from analysis. All patients were treated with the DIBH technique.

RT planning and delivery

The DIBH technique was performed using the Active Breathing Coordinator device (Elekta Oncology, Stockholm, Sweden), as previously described.[7,8] Patients underwent computed tomography simulation in the supine position with DIBH and during free breathing (FB) for comparison of dosimetry. Clinical target volumes and organs at risk were delineated on each FB and DIBH scan using standard methods.[10] The cardiac contour encompassed the skeletal muscle and pericardium. Three-dimensional conformal RT planning was performed with the XiO Planning System (Elekta, Maryland Heights, MO) with customized blocking of cardiac tissue. Dose distributions were calculated using a wedged tangential, 6- to 10-MV photons or forward-planned, "field-in-field" technique to achieve a ±5% dose gradient throughout the treatment volume. Dose-volume histograms were generated for comparison of dosimetry and the DIBH plan was ultimately used during the patient's radiation treatment if the MHD was reduced by 5% or greater. A separate breath hold was performed for treatment of each field. Following completion of RT, patients were reassessed every 3-6 months with history and physical examinations. Annual diagnostic mammography was performed in women with conserved breasts.

Modeled risk estimates and baseline risk estimates

The primary goal of this study was to use a current radiobiologic model to determine whether use of DIBH during RT for left-sided breast cancer reduces the risk of IHD, defined as myocardial infarction, coronary revascularization, or coronary death.[6] The excess risk of IHD from RT has been demonstrated to be linearly dependent on MHD at a rate of 16.3%, 15.5%, and 7.4% per Gy within years 0-4, 5-9, and 20-plus years following RT, respectively.[6] This model was used to determine modeled risk estimates (MRE) for each patient, while also incorporating patient-specific dosimetry and baseline risk estimates (BRE) for IHD at 5 and 10 years and throughout the patients' lifetime. Furthermore, MHD was expressed as equivalent dose in 2 Gy fractions (MHD_{EQD2}) using the equation $nd[(d+\alpha/\beta) \div (2+\alpha/\beta)]$, where n was the number of fractions, d was the dose to the heart per fraction, and α/β was 2 Gy.[6] Thus, the MRE for IHD at 5 years following RT can be expressed as: $MRE = BRE\,(1 + (0.163)(MHD_{EQD2}))$. Similarly, the MRE for the lifetime risk of IHD can be expressed as: $MRE = BRE\,(1 + (0.074)(MHD_{EQD2}))$.[6,11]

According to the Darby model, the excess risk of IHD is linearly dependent on MHD at a rate of 16.3% during years 0-4 and 15.5% during years 5-9 following breast RT.[6] To estimate MRE at 10 years, we used the more conservative estimate of 15.5% per Gy because this likely approximates the excess relative risk during years 0-9. Therefore, the MRE for IHD at 10 years can be expressed as: $MRE = BRE\,(1 + (0.155)(MHD_{EQD2}))$.

Patients were classified into American Heart Association (AHA) risk groups (Table 1), which are accessible to physicians and identify cardiac risk with accuracy similar to that of the Framingham algorithm.[12,13] BRE for IHD at 5 years following RT were determined using data from the Atherosclerosis Risk in Communities (ARIC) Study.[14,15]